EXHIBIT 4

AUSTRALIA

Patents Act 1990

IN THE MATTER OF
US Patent Application No. 09/446,109
by The University of Queensland

EXHIBIT VBS-4

This is Exhibit VBS-4 referred to in the Statutory Declaration by Vivien Bedford Santer

dated 13th May 2004

Before me:

Sally Shrimpton

SALLY ANN SHRIMPTON
3rd Floor, 509 St. Kilda Rd, Melbourne 3004
A current practitioner within the meaning
of the Legal Practice Act 1996.

A person empowered to witness Statutory
Declarations under the laws of the Victoria,
Commonwealth of Australia

INFORMATION FOR
HEALTH PROFESSIONALS

Data Sheet

RHEUMACIN

Indomethacin

Presentation

25 mg Capsules: white OP body, white OP cap, size 3. Contents a white powder.

50 mg Capsules: white OP body, white OP cap, size 2. Contents a white powder.

75 mg Capsules: clear colourless body, clear yellow cap, size 2. Contents small off-white spheres.

Uses

Actions

RHEUMACIN (indomethacin) is a highly effective nonsteroidal anti-inflammatory medicine with marked analgesic and antipyretic properties.

INDOMETHACIN is a potent inhibitor of prostaglandin synthesis *in vitro*. Concentrations are reached during therapy which have been demonstrated to have an effect *in vivo* as well.

INDOMETHACIN has been shown to be effective anti-inflammatory agent, appropriate for long-term use in rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis.

INDOMETHACIN affords relief of symptoms; it has not been shown to alter the progressive course of the underlying disease.

INDOMETHACIN has been found effective in relieving the pain, reducing the fever, swelling, redness, and tenderness of acute gouty arthritis.

The prostaglandin-inhibitory effect of INDOMETHACIN has been shown to be useful in the relief of pain and associated symptoms of primary dysmenorrhoea.

Anti-inflammatory Action:

The anti-inflammatory activity of INDOMETHACIN was first demonstrated in animals, measuring the ability of the compound to inhibit either granuloma formation or oedema induced by subplantar injection of carrageenin in rats. The latter appears to correlate well with antirheumatic activity in humans. Assays of relative potency indicated that INDOMETHACIN was more potent than acetylsalicylic acid, phenylbutazone or hydrocortisone; the potency ratios differed with the test employed.

The inhibition of carrageenin-induced oedema by INDOMETHACIN is specific the compound failed to inhibit oedema induced by a variety of agents other than cargeenin, nor did it reduce oedema if the medicine was administered after the oedema had been established.

As with other anti-inflammatory agents, the mechanism of action of INDOMETHACIN is unknown. INDOMETHACIN is fully active in the absence of the adrenals and the activity is readily demonstrable by direct application of the compound to the site of action. Unlike anti-inflammatory steroids, INDOMETHACIN in intact animals did not affect the size of the adrenals or the thymus, nor did it retard gain in body weight; these are sensitive indications of adrenal activation. The anti-inflammatory activity of combinations of

INDOMETHACIN and a steroid was that of either medicine alone in comparable doses.

Experiments have shown INDOMETHACIN to have a favourable effect upon adjuvant-induced polyarthritis in rats; it was more active than phenylbutazone or acetylsalicylic acid in suppressing the delayed manifestations of disseminated arthritis. This response is said to correlate well with clinical antiarthritic activity.

Antipyretic Activity:

The antipyretic activity of INDOMETHACIN has been demonstrated in rabbits and rats injected with bacterial pyrogen, and in the classical yeast-induced fever assay in rats.

A direct comparison of peak antipyretic activity in the yeast fever test showed INDOMETHACIN to be about nine times as potent as aminopyrine, 24 times as potent as phenylbutazone, and 43 times as potent as acetylsalicylic acid.

The antipyretic activity of INDOMETHACIN has been confirmed clinically by observations in patients with a variety of febrile conditions.

Analgesic Activity:

INDOMETHACIN is active in animal tests designed to assay analgesic activity of non-narcotic analgesics. Moderate doses raise the response threshold when pressure is applied to the yeast-inflamed foot of the rat, but do not affect responses to thermal stimuli, or to pressure on a non-inflamed foot. Qualitatively, INDOMETHACIN behaves like an analgesic of the anti-inflammatory/antipyretic type typified by the salicylates, and not of the narcotic type typified by morphine.

When single oral doses of INDOMETHACIN were assayed in the inflamed foot assay, the compound was found to be about 28 times as potent as acetylsalicylic acid and about 14 times as potent as phenylbutazone.

Pharmacokinetics

INDOMETHACIN is well absorbed after oral administration in all animals. In dogs, monkeys and rats, peak plasma levels after an oral dose occur within 0.5 to 2 hours.

The route of excretion is related to the species of animal and is independent of the route of administration or size of dose. Nearly all the compound or medicine-related metabolites could be recovered in urine and faeces. The rabbit eliminates INDOMETHACIN almost entirely in the urine, while the dog excretes nearly all the compound in the faeces. The rat, guinea pig, and monkey eliminate it by both routes.

In rabbits, rats, guinea pigs, and monkeys some INDOMETHACIN is metabolised by deacylation or demethylation and the metabolites are excreted as such or as the glucuronide conjugate.

Clinical Studies:

Prostaglandins sensitise afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Moreover, prostaglandins are known to be among the mediators of inflammation. Since INDOMETHACIN is an inhibitor of prostaglandin synthesis, the mode of action may be due to a decrease of prostaglandins in peripheral tissues.

In patients treated with INDOMETHACIN for rheumatoid arthritis and osteoarthritis, the anti-inflammatory action of INDOMETHACIN has been shown by reduction in joint swelling, reduction in pain, reduction in duration of morning stiffness, reduction in disease activity as assessed by both the investigator and patient; and by improved functional capacity as demonstrated by an increase in grip strength, and a decrease in time to walk 50 feet.

Following single oral doses of Capsules INDOMETHACIN 25 mg or 50 mg, INDOMETHACIN is readily absorbed, attaining peak plasma concentrations of approximately 1 and 2 mcg/ml, respectively, at about 2 hours. Orally administered Capsules INDOMETHACIN are virtually 100% bioavailable, with 90% of the dose absorbed within 4 hours.

Capsules INDOMETHACIN SR 75 mg are designed to release 25 mg of the medicine initially and the remaining 50 mg over approximately 12 hours (90% of dose absorbed by 12 hours). When measured over a 24 hour period, the cumulative amount and time-course of INDOMETHACIN absorption from a single Capsule

INDOMETHACIN SR are comparable to those of 3 doses of 25 mg Capsules INDOMETHACIN given at 4-6 hour intervals.

Plasma concentrations of INDOMETHACIN fluctuate less and are more sustained following administration of Capsules of INDOMETHACIN SR than following administration of 25 mg Capsules INDOMETHACIN given at 4-6 hour intervals. In multiple-dose comparisons, the mean daily steady-state plasma level of INDOMETHACIN attained with daily administration of Capsules INDOMETHACIN SR 75 mg was indistinguishable from that following Capsules INDOMETHACIN 25 mg given at 0, 6 and 12 hours daily. However, there was a significant difference in INDOMETHACIN plasma levels between the two dosage regimens, especially after 12 hours.

Controlled clinical studies in patients with osteoarthritis have shown that one Capsule INDOMETHACIN SR was clinically comparable to one 25 mg Capsule INDOMETHACIN t.i.d; and in controlled clinical studies in patients with rheumatoid arthritis, one Capsule INDOMETHACIN SR taken in the morning and one in the evening were clinically indistinguishable from one 50 mg Capsule INDOMETHACIN t.i.d.

INDOMETHACIN is eliminated via renal excretion, metabolism, and biliary excretion. INDOMETHACIN undergoes appreciable enterohepatic circulation. The mean half-life of INDOMETHACIN is estimated to be about 4.5 hours. With a typical therapeutic regimen of 25 or 50 mg t.i.d, the steady-state plasma concentrations of INDOMETHACIN are an average 1.4 times those following the first dose.

INDOMETHACIN exists in the plasma as the parent medicine and its desmethyl, desbenzoyl, and desmethyl-desbenzoyl metabolites, all in the unconjugated form. About 60% of an oral dosage is recovered in urine as medicine and metabolites (26% as INDOMETHACIN and its glucuronide), and 33% is recovered in faeces (1.5% as INDOMETHACIN).

About 90% of INDOMETHACIN is bound to protein in plasma over the expected range of therapeutic plasma concentrations.

Indications

RHEUMACIN is indicated in active stages of:

1. Rheumatoid arthritis
2. Osteoarthritis
3. Degenerative joint disease of the hip
4. Ankylosing spondylitis
5. Acute gouty arthritis

It is also included for:

Acute musculoskeletal disorders, such as bursitis, tendonitis, synovitis, tenosynovitis, capsulitis of the shoulder, sprains and strains.

Low back pain (commonly referred to as lumbago).

Fever (as a short-term adjunct to specific therapy).

Inflammation, pain, trismus and swelling following dental procedures.

Inflammation, pain and swelling following orthopaedic surgical procedures and nonsurgical procedures associated with reduction and immobilisation of fractures or dislocations.

Pain and associated symptoms of primary dysmenorrhoea.

Dosage and Administration

Dolonex* Gel

(Piroxicam)

DESCRIPTION

Dolonex, brand of piroxicam, is a member of the chemical class of nonsteroidal anti-inflammatory drugs (NSAIDs), the oxicams. Piroxicam is an amphoteric compound. It occurs as a white to off-white crystalline solid, poorly soluble in water, dilute acid, and most organic solvents. It is slightly soluble in alcohols and in aqueous alkaline solution.

Dolonex 0.5% Gel is available as a clear pale yellow gel.
Each gram of gel contains piroxicam USP 5 mg

Inert excipients include: ethyl alcohol, benzyl alcohol, propylene glycol, carbopol 940, di-isopropanolamine, hydroxyethyl cellulose, and water.

ACTIONS

Dolonex Gel is a nonsteroidal anti-inflammatory (NSAID) agent which also possesses analgesic properties. Edema, erythema, tissue proliferation, fever and pain can all be inhibited in laboratory animals by the administration of Dolonex Gel.

Acute and chronic toxicity and irritation studies have been carried out in animals. In an acute study, albino rats were given a single dermal application of 5g/kg (200 - 300 times the recommended clinical application). No deaths, toxic signs or skin irritation were observed and no gross changes were found at autopsy. A one month study was conducted in albino rats. One group received a daily application of gel to dorsal skin of 1 g per rat, another was treated with the vehicle and the third group served as untreated controls. No skin irritation was noted at the treatment sites, and no drug-related changes were observed in hemotology, laboratory chemistries, organ weight, autopsy findings or histopathology. The gel was also evaluated for primary skin irritation, eye irritation, and phototoxicity in rabbits, and for photoallergy and skin sensitization potential in guinea pigs, all according to standard established protocols. No skin reactions were found after application of 0.5% gel or the vehicle to intact rabbit skin. On abraded skin, piroxicam gel produced slight erythema and edema which was slightly greater than that following vehicle.

The anti-inflammatory and analgesic effects of Dolonex 0.5% Gel were studied in rats and guinea pigs using such standard models of pain and inflammation as carrageenin induced rat paw edema, ultraviolet erythema in guinea pigs, traumatic edema in rats, yeast induced pain in rats, croton oil induced erythema on guinea pigs abdomens, cotton pellet induced granuloma formation in rats and adjuvant induced arthritis in rats. Dolonex 0.5% Gel was comparable to indomethacin 1% gel in all of these models and was comparable to orally administered piroxicam in inhibiting inflammation in the rat paw edema model.

On the basis of various pharmacokinetic and tissue distribution studies in rats and dogs, piroxicam 0.5% gel is continuously and gradually released from the skin to underlying muscle or synovial fluid. In addition, equilibrium between skin and muscle or synovial fluid appears to be reached rapidly, within a few hours after application.

A multiple dose study of twice-daily application of piroxicam 0.5% gel (total daily dose equivalent to 20 mg per day, piroxicam) for 14 days found that plasma levels rose slowly over the course of the treatment period and reached a value of over 200 ng/ml on the 4th day. On average, steady state plasma levels were between 300 and 400 ng/ml and mean values remained below 400 ng/ml even on the 14th day of treatment. These piroxicam levels observed at equilibrium were approximately 5% of those observed in subjects receiving similar oral dosing (20 mg daily). Elimination half-life in this study was calculated to be approximately 79 hours. In humans, the gel was well tolerated in skin sensitive volunteers.

INDICATIONS

Dolonex Gel is indicated for a variety of conditions characterized by pain, inflammation and stiffness, such as osteoarthritis (arthrosis, degenerative joint disease) of superficial joints such as the knee, post-traumatic or acute musculoskeletal disorders including tendonitis, tenosynovitis, periarthritis, sprains, strains and low back pain.

CONTRAINDICATIONS

1. Dolonex Gel should not be used in those patients who have previously shown a hypersensitivity to the gel or piroxicam in any of its dosage forms. The potential exists for cross sensitivity to aspirin and other nonsteroidal anti-inflammatory drugs.

2. Dolonex Gel should not be given to patients in whom aspirin and other nonsteroidal anti-inflammatory drugs induce the symptoms of asthma, rhinitis, angioedema or urticaria.

Dolonex* Gel

(Piroxicam)

WARNINGS

Use in Pregnancy and in Nursing Mothers: Although no teratogenic effects were seen when Dolonex was orally administered in animal testing, the safety of Dolonex use during pregnancy or during lactation has not yet been established. Dolonex inhibits prostaglandin synthesis and release through a reversible inhibition of the cyclo-oxygenase enzyme. This effect, as with other nonsteroidal anti-inflammatory agents has been associated with an increased incidence of dystocia and delayed parturition in pregnant animals when drug administration was continued into late pregnancy. Nonsteroidal anti-inflammatory drugs are also known to induce closure of the ductus arteriosus in infants.

The presence of piroxicam in breast milk has been determined during initial and long term dosing conditions (52 days). Piroxicam appeared in breast milk at about 1% to 3% of the maternal plasma concentrations. No accumulation of piroxicam occurred in milk relative to that in plasma during treatment. Dolonex gel is not recommended for use in nursing mothers as the clinical safety has not been established.

Use in Children: Dosage recommendations and indications for use in children have not been established.

PRECAUTIONS

If local irritation develops, the use of the gel should be discontinued and appropriate therapy instituted as necessary. Do not apply to the eyes, mucosal surfaces, or to any sites affected by open skin lesions, dermatoses, or infections.

ADVERSE REACTIONS

Side effects possibly related to treatment have been infrequently reported. In clinical trials the vast majority of side effects involved mild or moderate local irritation, erythema, rash, pityroid desquamation, pruritus, and related local reactions at the application site. Mild but transient skin discoloration and staining of clothing have been noted when the gel is not rubbed in completely.

OVERDOSAGE

Overdosage is unlikely to occur with this topical condition.

Dolonex* Gel

(Piroxicam)

DOSAGE AND ADMINISTRATION

This product is intended for external use only. No occlusive dressing should be employed. Rub in the gel leaving no residual material on the skin.
A dosage of one gram, equivalent to 5 mg of piroxicam (corresponding to approximately 3 cm or 1¼") should be applied to the affected site three or four times per day. Therapy should be reviewed after 4 weeks.

SUPPLY

Dolonex 0.5% Gel: Tubes of 15g and 50g.

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